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Diagnostic Laboratory Markers for Spontaneous Bacterial Peritonitis

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Abstract

Spontaneous bacterial peritonitis (SBP) is an often-life-threatening bacterial infection in patients with liver cirrhosis with ascites. Useful laboratory methods for early diagnosis are essential. The gold standard method for the diagnosis of SBP is a polymorphonuclear leukocyte (PMN) count of ≥250 cells/mm^3 in the ascitic fluid. Some studies have investigated the usefulness of other novel laboratory methods for the diagnosis of SBP. This paper reviews studies of diagnostic markers for SBP, such as procalcitonin, calprotectin, and leukocyte esterase reagent strips in ascitic fluid. At present, serum procalcitonin is a relatively sensitive and specific marker for the diagnosis of SBP. The usefulness of ascitic levels of procalcitonin and calprotectin for differentiating between SBP and sterile ascites is still uncertain because of the small number of studies. Although the sensitivity of leukocyte esterase reagent strips for diagnosing SBP is variable, a negative test result may predict absence of SBP.

Keywords: Spontaneous bacterial peritonitis; Procalcitonin; Calprotectin; Leukocyte esterase reagent strips

Abbreviations: CRP: C-Reactive Protein; ELISA: Enzyme-Linked Immunosorbent Assay; IL-6: Interleukin-6; IP-10: Interferon-γ-Induced Protein; LC: Liver Cirrhosis; MIP-1β: Macrophage Inflammatory Protein Type 1 Beta; PMN: Polymorphonuclear Cell; SBP: Spontaneous Bacterial Peritonitis; TNF-α: Tumor Necrosis Factor-α; TREM-1: Triggering Receptors Expressed on Myeloid Cells

Introduction

Patients with liver cirrhosis (LC) are at high risk for bacterial infections [1,2]. It has been reported that 30% to 60% of inpatients with LC develop a bacterial infection [1,3], and the incidence of bacterial infections in patients with LC is 4-5-fold higher than that in the general population [3]. Among patients with LC accompanied by bacterial infections, spontaneous bacterial peritonitis (SBP) is the most common complication (10% to 30% cases) and often life-threatening, with mortality among ranging from 10% to 46% [4]. The incidence of SBP caused by multidrug-resistant bacteria has increased in recent decades and has been associated with higher mortality [3,5,6]. The diagnosis of SBP in patients with LC is not always straightforward because SBP is sometimes asymptomatic, and a delay in the diagnosis often leads to fatal outcomes, including sepsis or multiple organ failure [2,7,8].

The gold standard method for the diagnosis of SBP is a polymorphonuclear cell (PMN) count of ≥250 cells/mm^3 in the ascitic fluid, regardless of bacterial isolation [1,4,9]. However, paracentesis is not always possible and can sometimes be too time-consuming for an early diagnosis of SBP [10]. Therefore, novel and useful biomarkers for early diagnosis of SBP are desirable. Laboratory methods for early prediction of response to the first treatment are also desirable because nonresponse to the first treatment is a predictor of mortality accompanied with SBP [11]. The present article reviews and summarizes previous studies of laboratory markers in the serum and ascitic fluid for diagnosis of SBP.

Diagnosis of SBP

SBP is defined as a bacterial infection of the ascitic fluid without any apparent intraabdominal source of infection or malignancy [2]. This definition thus excludes infectious pleural effusion, peritonitis carcinomatosa, and hemorrhagic ascites such as hepatocellular carcinoma rupture. As stated earlier, SBP is diagnosed in patients with a PMN count of ≥250 cells/mm^3 in the ascitic fluid, regardless of bacterial isolation from the fluid [1,9]. The classic symptoms include fever, abdominal pain, and worsening of preexisting ascites, although up to one-third of SBP cases may be asymptomatic [12].

Possible Diagnostic Markers of SBP

The possible serum or ascitic fluid markers of SBP reported in previous studies, except for the gold standard method of PMN count in the ascitic fluid, are as follows **(Table 1)**.

Proinflammatory Cytokines

Bacterial endotoxins are the main stimulus for the production of several proinflammatory cytokines, such as tumor necrosis factor (TNF)-α and interleukin (IL)-6. In patients with SBP, TNF-α and IL-6 are released into the blood in

response to hepatic injury [13,14], and increases in these proinflammatory cytokines may be associated with renal impairment or death [13,15]. TNF-α and IL-6 levels in ascitic fluid are significantly higher in patients with SBP than in those with sterile ascites [13,16,17].

Table 1 The possible serum or ascitic fluid markers of spontaneous bacterial peritonitis reported in previous studies.

Possible markers	Reference
Serum	
Tumor necrosis factor-α	[13-16]
Interleukin-6	[13-16]
Procalcitonin	[13,17,21,28-31]
Interferon-induced protein 10 kDa	[16]
High-sensitivity CRP	[52]
Ascitic fluid	
Tumor necrosis factor-α	[13,16,17]
Interleukin-6	[13,16,17]
Lactoferrin	[4,19,20]
Calprotectin	[13,18,35]
Leukocyte esterase reagent strips	[4,5,10,36-48]
Macrophage inflammatory protein type 1 β	[21]
Interferon-γ-induced protein 10 kDa	[16]
Triggering receptor expressed on myeloid cells 1	[51]
High-sensitivity CRP	[53]

Lactoferrin

Lactoferrin is mainly produced by neutrophilic granulocytes and could therefore be a possible marker of PMN activity [4,18]. Its presence in body fluids is proportional to the flux of neutrophils [4,19]. Previous studies showed that ascitic lactoferrin concentration was significantly increased in patients with SBP [4,19,20]. Although lactoferrin detected in ascitic fluid has shown high sensitivity and specificity for the diagnosis of SBP [4], the timing of quantitative measurements remains to be clarified, and diagnostic test kits to measure lactoferrin are not yet commercially available [4,18].

Procalcitonin

Procalcitonin in patients with LC

Procalcitonin, a 116-amino-acid prohormone of calcitonin, is synthesized in the C cells of the thyroid gland. Procalcitonin levels can be measured using enzyme-linked immunosorbent assay (ELISA) [13] or immunofluorescence method [21]. The current reference value (a cutoff value) is estimated to be approximately 0.5 ng/mL in healthy populations [22,23]. Procalcitonin is a well-known acute phase reactant protein as well as a C-reactive protein (CRP) [24]. Release of procalcitonin during infection may be induced directly by microbial toxins and indirectly by humoral factors or a cell-mediated host response [23]. Therefore, procalcitonin is a useful marker in the diagnosis of systemic bacterial infections. The liver is a major source of procalcitonin and CRP [25]. However, Bota et al. [25] reported that serum procalcitonin levels in patients with LC with bacterial infection were not significantly lower than those in non-LC patients with bacterial infection. Moreover, many studies have indicated that serum procalcitonin levels are significantly higher in patients with LC with bacterial infections (excluding SBP) than in those without bacterial infections [26,27]. Therefore, serum procalcitonin levels are being considered as a marker for early diagnosis of bacterial infections in both LC and non-LC patients [22,24].

Serum and ascitic procalcitonin levels in patients with LC with SBP

Although the usefulness of serum or ascitic procalcitonin levels for diagnosis of SBP in patients with LC has been investigated, large-scale studies have been limited. Seven studies have looked at serum procalcitonin levels [13,17,21,28-31] and three at ascitic fluid procalcitonin levels [17,21,31].

Six of seven studies reported that serum procalcitonin levels were significantly higher in patients with SBP than in those with sterile ascites [13,17,28-31]. Only one study reported no significant differences in serum procalcitonin levels between patients with SBP and those with sterile ascites [21]. However, this study included only 10 SBP cases and therefore the relevance of its findings is limited. The results of previous studies of serum procalcitonin levels of patients with LC accompanied by SBP suggest that serum procalcitonin is a sensitive marker for diagnosing SBP. Cutoff values of 0.46 ng/mL to 0.94 ng/mL are suggested for differentiating between SBP and sterile ascites [13,17,22,28-30]. According to Yuan et al. [29], a cutoff value of 0.48 ng/mL is a better marker than white blood cell count in peripheral blood for diagnosing SBP in hepatitis B virus-infected patients with LC. According to Cekin et al. [28], a procalcitonin cutoff value of 0.61 ng/mL is a good marker for diagnosing SBP and is more accurate than serum CRP. Yang et al. [32] analyzed seven previous publications [17,21,22,28-31] reporting serum procalcitonin levels of 339 patients with LC accompanied by SBP and concluded that serum procalcitonin is a relatively sensitive and specific test for the diagnosis of SBP.

Of the three reports that investigated procalcitonin levels in ascitic fluid, two found no significant differences in procalcitonin levels between patients with SBP and those with sterile ascites [21,31]. However, two of these studies included only 10 SBP cases, limiting the relevance of their findings. The remaining study reported that ascitic fluid procalcitonin levels in patients with SBP were significantly higher than those in patients with sterile ascites, but that ascitic fluid procalcitonin levels were less accurate than IL-6 levels for the diagnosis of SBP [17]. However, the usefulness of ascitic fluid procalcitonin

level for differentiating between SBP and sterile ascites is still uncertain because of the small number of studies.

Calprotectin

Over the past 20 years, the use of calprotectin has evolved as a noninvasive biomarker of gastrointestinal inflammation [18,33]. Calprotectin is a calcium- and zinc-binding protein with antimicrobial and antiproliferative functions, which is detected almost exclusively in neutrophils; its presence in body fluids is proportional to the influx of neutrophils [13,18,34]. Calprotectin levels can be measured using assay ELISA [13,18,34]. Burri et al. [34] reported that measurement of calprotectin in ascetic fluid correlated well with the PMN count and reliably predicted a level of ≥250 cells/mm^3 in the ascitic fluid, which is the standard marker for the diagnosis of SBP. The usefulness of ascitic calprotectin levels for diagnosis of SBP in patients with LC has been reported. Recent studies (2015~2016) have indicated that ascitic calprotectin levels are significantly higher in patients with LC with SBP than in those without SBP [13,18,35]. Fernandes et al. [35] reported that a cutoff value of 1.57 μg/mL was a good predictor of SBP. Lutz et al. [18] showed that the ratio of calprotectin to total protein in the ascitic fluid was a better diagnostic marker for SBP than calprotectin alone, and that a high ratio of calprotectin to total protein in the ascitic fluid was an independent predictive factor of 30-day mortality. Abdel-Razik et al. [13] showed that a cutoff value of 0.445 μg/mL was a good predictor of SBP. However, the usefulness of the ascitic fluid calprotectin level for differentiating between SBP and sterile ascites is still uncertain because of the small number of studies.

Leukocyte Esterase Reagent Strips

Leukocyte esterase reagent strips, which detect leukocyte esterase activity in biological fluids, are a very rapid and inexpensive method of diagnosing SBP [4,5,10,36-38]. They were first used for urine analysis, but they recently have been found useful across a wide range of body fluid infections [39,40]. In the past two decades, several studies have examined the usefulness of leukocyte esterase reagent strips for the diagnosis of SBP. Oey et al. [38] summarized 23 studies published from 2002 to 2015 and concluded that the accuracy of the strips for the diagnosis of SBP varied, with a sensitivity of 45% [41] to 100% [38,42], a specificity of 90% to 100% [43], a positive predictive value of 42% [44] to 100% [43], and a negative predictive value of 93% [45] to 100% [38,42]. Thus, leukocyte esterase reagent strips have poor sensitivity and poor positive predictive value [4,37,38]. The authors also concluded that although the sensitivity of the strips for diagnosing SBP was variable, a negative test result strongly predicted the absence of SBP [38,42]. Koulaouzidis [37] summarized 26 studies published from 2002 to 2010 regarding the usefulness of leukocyte esterase reagent strips and concluded that the strips had poor sensitivity (45% [41] to 100% [42]) and poor positive predictive value (37% [46] to 100% [43,47,48]), but high negative predictive value (93% [45] to 100% [10,42]). Two recent studies also indicated that the strips were useful for excluding SBP, with high negative predictive values [39,40].

Macrophage Inflammatory Protein Type 1 Beta

Macrophage inflammatory protein type 1 beta (MIP-1β) is an acidic protein composed of 69 amino acids [21]. It belongs to the family of chemokines, which are well known for their chemotactic and proinflammatory effects [21]. Although MIP-1β levels can be measured using ELISA [21], the usefulness of MIP-1β for the diagnosis of bacterial infections in patients with LC is unclear [21]. The possible usefulness of ascites MIP-1β levels for the diagnosis of SBP was reported by Lesińska et al. [21]. The authors showed that ascitic MIP-1β levels were significantly higher in patients with SBP than in those without SBP, whereas there was no significant difference in serum MIP-1β levels between patients with and without SBP [21]. However, the number of studies on the diagnostic usefulness of MIP-1β is still limited.

Interferon-γ-Induced Protein

Interferon-γ-induced protein 10 kDa (IP-10) is one of the well-studied biomarkers of infection. It is involved in multiple biological functions, inducing chemotaxis, apoptosis, recruiting activated T-cells, macrophages, and natural killer (NK) cells to sites of infection [49]. IP-10 levels can be measured using ELISA [16]. The possible usefulness of IP-10 in the serum and ascitic fluid for diagnosing SBP was reported by Abdel-razik et al. [16]. The authors showed that serum and ascitic IP-10 levels were significantly higher in patients with SBP than in those without SBP. However, the number of studies on the diagnostic usefulness of IP-10 is still limited.

Triggering Receptor Expressed on Myeloid Cells 1

Triggering receptor expressed on myeloid cells 1 (TREM-1) is a receptor expressed and released by innate inflammatory cells after exposure to bacterial membrane components [50]. TREM-1 levels can be measured using ELISA [51]. TREM-1 was recently suggested as a possible diagnostic marker for SBP, although there is little evidence for its usefulness at present. Ichou et al. [51] reported that ascitic TREM-1 concentration was significantly higher in patients with SBP than in those without SBP and that TREM-1 was a strong, sensitive, and specific marker for the diagnosis of SBP.

High-Sensitivity (Sensitive) C-Reactive Protein

The high-sensitivity C-reactive protein (hs-CRP) assay can detect much lower levels of CRP than the traditional methods [52]. Guler et al. [52] reported that serum levels of hs-CRP were significantly higher in patients with SBP than in those with sterile ascitic fluid. The authors also reported that these

levels promptly decreased after 2 days of administration of antimicrobial agents, indicating that the serum level of hs-CRP may be a useful marker for the prediction of response to the first treatment. Kadam et al. [53] recently reported that the mean level of hs-CRP in ascitic fluid was significantly higher in patients with SBP than in those without SBP and was also higher in patients with SBP with poor outcomes. However, the number of studies on the diagnostic usefulness of hs-CRP is still limited.

Conclusion

SBP often presents life-threatening complications in patients with LC. Although a PMN count ≥250 cells/mm^3 in the ascitic fluid is the gold standard for diagnosis of SBP, establishment of other laboratory methods for early diagnosis and prediction of response to the first treatment is essential. This article reviews and summarizes recent studies of diagnostic markers for SBP. The number of studies is limited. Further studies with larger numbers of patients will be necessary to evaluate the usefulness of markers for the early diagnosis of SBP and prediction of response to the first treatment of SBP.

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